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EXPEDITED REVIEW

Corrected QT Variability in Serial Electrocardiograms in Long QT Syndrome

The Importance of the Maximum Corrected QT for Risk Stratification

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OBJECTIVES We evaluated the incremental prognostic information provided by multiple corrected QT (QTc) measurements on serial electrocardiograms (ECGs) in patients with the inherited long QT syndrome (LQTS).

BACKGROUND A baseline QTc of ≥500 ms has been shown to be associated with increased risk of cardiac events among LQTS patients. However, the value of QTc measurements on follow-up ECGs in risk assessment has not been determined.

METHODS The risk of a first LQTS-related cardiac event during adolescence was assessed in 375 patients enrolled in the International LQTS Registry for whom serial follow-up ECGs were recorded before age 10.

RESULTS The mean ± SD difference between the minimum and maximum QTc values on serial ECGs recorded in study patients was 47 ± 40 ms. The maximum QTc interval recorded before age 10 was the strongest predictor of cardiac events during adolescence (adjusted hazard ratio [HR] = 2.74; $p < 0.001$). Other follow-up QTc measures, including the baseline, the mean, and the most recent QTc interval recorded before age 10, were less significant risk factors. After adjusting for the maximum QTc value during follow-up, no significant association remained between the baseline QTc value and the risk of subsequent cardiac events (HR = 1.04; $p = 0.91$).

CONCLUSIONS In LQTS patients, there is a considerable variability in QTc measures in serial follow-up ECGs. The maximum QTc interval provides incremental prognostic information beyond the baseline measurement. We suggest that risk stratification in LQTS patients should include follow-up ECG data. (J Am Coll Cardiol 2006;48:1047–52) © 2006 by the American College of Cardiology Foundation

Congenital long QT syndrome (LQTS) is a genetic disorder that leads to the prolongation of the cardiac action potential duration and is clinically manifest by increased duration of the heart rate-corrected QT (QTc) interval on the surface electrocardiogram (ECG) (1–3).

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A baseline QTc interval of ≥500 ms has been shown to be associated with a high risk of cardiac events (syncope, aborted cardiac arrest, or LQTS-related death) in LQTS patients (4–8). However, the relationship between the QTc interval duration and the risk of cardiac events in earlier studies was evaluated primarily for the first recorded ECG, and the incremental prognostic information provided by follow-up ECGs has not been determined.

In the current study, we assessed the value of follow-up ECG data recorded before age 10 years in predicting subsequent cardiac events during adolescence, a time period known to be associated with a high rate of LQTS-related events (2).

METHODS

Study population. The study population was drawn from the International LQTS Registry and involved subjects from proband-identified families diagnosed with LQTS by prolonged QTc criteria for age and gender as previously reported (4). The present analysis comprised 375 patients for whom ≥2 ECGs were recorded before age 10 years and follow-up data on cardiac events that occurred between 10 and 20 years of age were available.

Data collection and management. For each patient, data on personal and family history, cardiac events, and therapy were systematically recorded at each visit or medical contact. Clinical data were recorded on prospectively designed forms

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Abbreviations and Acronyms

ACA = aborted cardiac arrest
ECG = electrocardiogram
HR = hazard ratio
LQTS = long QT syndrome
QTc = corrected QT

and included patient and family history and demographic, ECG, therapeutic, and cardiac event information. Upon enrollment in the Long QT Registry, a 12-lead ECG was obtained from each patient. From this first recorded ECG, the duration of the QT interval was assessed from lead II (or lead I or III if the QT interval could not be measured from lead II) and corrected for heart rate using Bazett's formula (9). Additional serial QTc recordings were obtained from ECGs recorded during follow-up contacts, usually at yearly intervals. Electrocardiograms were excluded from the analysis if recorded within 1 month after a previous ECG or within 1 month after an LQTS-related cardiac event. The reported analyses used the LQTS analytic database version 13.

All subjects or their guardians provided informed consent to inclusion in the registry and subsequent clinical studies.

QTc summary measures. To evaluate the prognostic implications of follow-up ECG data, we examined the following QTc summary measures: 1) the QTc value obtained from the first recorded ECG (baseline QTc); 2) the average of all recorded QTc values before age 10 (mean QTc); 3) the highest QTc value obtained at any time before age 10 (maximum QTc); and 4) the QTc value obtained from the last ECG recorded before age 10 (recent QTc). In the primary analysis, QTc summary measures were dichotomized at 500 ms, a value shown in previous studies to be associated with increased risk of cardiac events in LQTS patients (4–8); to avoid bias created by the possibility that the 500 ms threshold is not optimal for all of the summary measures, an alternative analysis was carried out in which each QTc summary measure was dichotomized at its upper tertile, resulting in an equal number of positive tests for each QTc summary measure. In a secondary analysis, we assessed the relationship between different QTc thresholds and the risk of cardiac events in study patients.

Because the cube root Fridericia formula has been suggested to reflect a more accurate correction factor than Bazett's formula in subjects with faster heart rates (10), including children, all QTc analyses were repeated using the Fridericia rate correction.

Cardiac events and medical therapy during follow-up. Data regarding LQTS-related cardiac events was prospectively collected and included the date of unexplained syncope, aborted cardiac arrest (ACA) requiring cardiac resuscitation, and unexpected sudden death exclusive of a known cause before age 21 years.

In the present analysis the end point was defined as the occurrence of a first cardiac event (syncope, ACA, or LQTS-related death) between 10 and 20 years of age.

Follow-up data regarding beta-blocker therapy included the starting date, type of beta-blocker, and discontinuation date in case it occurred. Among patients who died, the usage of a beta-blocker before death was determined retrospectively.

Statistical analysis. The distribution of the time to first cardiac event during adolescence, stratified by QTc summary measures obtained before age 10, was estimated using the Kaplan-Meier method.

Cox proportional hazards regression was used to determine the significant and independent contribution of each QTc summary measure to the development of a first cardiac event during adolescence. Additional covariates in each model included time-dependent beta-blocker therapy, the occurrence of a nonfatal cardiac event before age 10 years, and the number of follow-up ECGs obtained before age 10 years (considered as either a linear or a categoric [2, 3, or ≥4 ECGs] variable), and the age of the first recorded ECG. The deviance (−2 log likelihood) was used to determine and compare the fit of each QTc summary measure model, with the model with the best fit having the lowest deviance.

In the analysis of the association between different QTc thresholds and cardiac events, a number of variables representing QTc duration dichotomized at different values (from 480 ms to 540 ms at 10-ms intervals) were analyzed to identify the best QTc threshold. A best subsets procedure for proportional hazards regression was used to compare the model fit using the different QTc thresholds. All of these models included the covariates for time-dependent beta-blocker use, cardiac events before the age of 10 years, the number of recorded ECGs before age 10 years and the age of the first recorded ECG.

A significance level of 0.05 was used for declaring statistical significance of 2-sided tests. The statistical software used for the analyses was SAS version 9.13 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline clinical and ECG characteristics and cardiac events during follow-up are shown in Table 1. Among the 375 study subjects, the proportion of boys and girls was similar and more than one-half were treated with beta-blockers before age 10 years. A total of 99 study patients were genetically tested and identified as carriers of an LQTS mutation (LQT1: 55 patients; LQT2: 32 patients; LQT3: 11 patients; and LQT6: 1 patient).

Syncope occurred in 30% of patients before the age of 10 and was the most frequent cardiac event during adolescence.

The QTc interval duration exhibited considerable variation when follow-up ECGs were evaluated. The mean ± SD difference between the minimum and maximum QTc values recorded in study patients before age 10 years was 47

Table 1. Baseline Clinical and ECG Characteristics Before Age 10 Years and Frequency of Cardiac Events During Adolescence

Parameter	n = 375
Baseline clinical characteristics	
Female gender, n (%)	176 (47%)
Beta-blocker before age 10	202 (54%)
Hearing loss, n (%)	13 (3%)
Syncope before age 10, n (%)	113 (30%)
ACA before age 10, n (%)	20 (5%)
ECG data before age 10	
Age of first recorded ECG, yrs (mean ± SD)	4.2 ± 3.3
Time interval between ECGs, yrs (mean ± SD)	1.5 ± 1.6
Number of ECGs (mean ± SD)	3.8 ± 2.8
Heart rate per ECG, beats/min (mean ± SD)*	89 ± 20.3
QTc summary measures (ms)	
Baseline QTc (mean ± SD)	471 ± 56
Mean QTc (mean ± SD)	467 ± 48
Maximum QTc (mean ± SD)	495 ± 64
Recent QTc (mean ± SD)	465 ± 55
QTc ≥500 ms	
Baseline, n (%)	95 (25%)
Mean, n (%)	85 (23%)
Maximum, n (%)	152 (41%)
Recent, n (%)	94 (25%)
Events during adolescence	
Syncope, n (%)	54 (14%)
ACA, n (%)	4 (1%)
LQTS death, n (%)	12 (3%)

*Value is given as the mean heart rate in all ECGs recorded before age 10.
ACA = aborted cardiac arrest; ECG = electrocardiogram/electrocardiographic; LQTS = long QT syndrome; QTc = corrected QT.

± 40 ms, and the maximum QTc was longer than baseline, mean, and recent QTc values by 24 ms, 28 ms, and 30 ms, respectively. When QTc summary measures were dichotomized at 500 ms, the maximum QTc measure was shown to indicate the highest proportion of patients with a value of ≥500 ms (41%), whereas the proportion of such patients indicated by baseline, mean, and recent QTc values of ≥500 ms was lower (25%, 23%, and 25%, respectively).

Association between QTc summary measures before age 10 years and cardiac events during adolescence. Adjusted hazard ratios (HRs) for cardiac events during adolescence for each QTc summary measure dichotomized at 500 ms are shown in Table 2A. After adjusting for time-dependent beta-blocker therapy, cardiac events before age 10, the number of ECGs recorded before age 10, and the age of the first recorded ECG, baseline QTc of ≥500 ms was an insignificant risk factor for cardiac events during adolescence, whereas follow-up QTc summary measures were stronger and significant risk factors. Among the 4 QTc summary measures analyzed, a maximum QTc value of ≥500 ms was the most significant predictor of cardiac events during adolescence. Accordingly, model 3, in which the maximum QTc summary measure was included as covariate, was shown to have the best fit (as defined by the lowest deviance [−2 log likelihood]) of the 4 models (Table 2A).

In an alternative analysis, each QTc summary measure was dichotomized at its upper tertile. Similar results were obtained (Table 2B), demonstrating that the maximum QTc was the most significant risk predictor among the four summary measures. Notably, dichotomizing the QTc summary measures resulted in superior fit to the data (as measured by the deviance), compared with entering summary QTc measures as continuous covariates, suggesting that an assumption of linearity on the log hazard scale is not well supported by the data.

To further evaluate the relative importance of baseline and follow-up QTc summary measures, we included two QTc summary measures, dichotomized at the upper tertile, in each Cox model, resulting in 6 different combinations of QTc measures. Consistent results were demonstrated, showing that when the maximum QTc was combined with each of the other 3 QTc summary measures, only the former QTc parameter was associated with a significant increase in the risk of cardiac events (maximum QTc + baseline QTc: HR = 2.70 [p = 0.006] and 1.04 [p = 0.91], respectively; maximum QTc + mean QTc: HR = 2.54 [p = 0.04] and 1.11 [p = 0.84], respectively; maximum QTc + recent QTc: HR = 3.28 [p < 0.001] and 0.76 [p = 0.41], respectively). Accordingly, models including the maximum QTc as one of the summary measures maintained the best fit for predicting subsequent cardiac events.

Similar results were obtained when QTc was calculated using the Fridericia formula (data not shown). However, the

Table 2. Adjusted Hazard Ratios for Cardiac Events for the 4 QTc Summary Measures*

A. Summary Measures Dichotomized at 500 ms

QTc Summary Measures	HR	95% Confidence Interval	p Value
Model 1:			
Baseline QTc	1.53	0.88–2.68	0.13
Model 2:			
Mean QTc	2.09	1.18–3.72	0.01
Model 3:†			
Maximum QTc	2.74	1.52–4.85	<0.001
Model 4:			
Recent QTc	2.03	1.17–3.52	0.01

B. Summary Measures Dichotomized at the Upper Tertile‡

QTc Summary Measures	HR	95% Confidence Interval	p Value
Model 1:			
Baseline QTc	1.89	1.06–3.37	0.03
Model 2:			
Mean QTc	2.22	1.05–4.66	0.04
Model 3:†			
Maximum QTc	2.76	1.56–4.87	<0.001
Model 4:			
Recent QTc	1.21	0.67–2.21	0.52

*Each QTc summary measure was included separately in a Cox model and was further adjusted for the following covariates: time-dependent beta-blocker therapy, cardiac events before age 10, the number of ECGs recorded before age 10 and the age of the first recorded ECG; similar results were obtained when the number of ECGs recorded before age 10 was categorized (2, 3 or ≥4 ECGs). Gender did not make a significant contribution to outcome in the multivariate models. †Model with the best fit as defined by the lowest deviance (−2 log likelihood). ‡Dichotomized QTc values were as follows: baseline, mean, and recent: 480 ms; maximum: 510 ms.
HR = hazard ratio; other abbreviations as in Table 1.

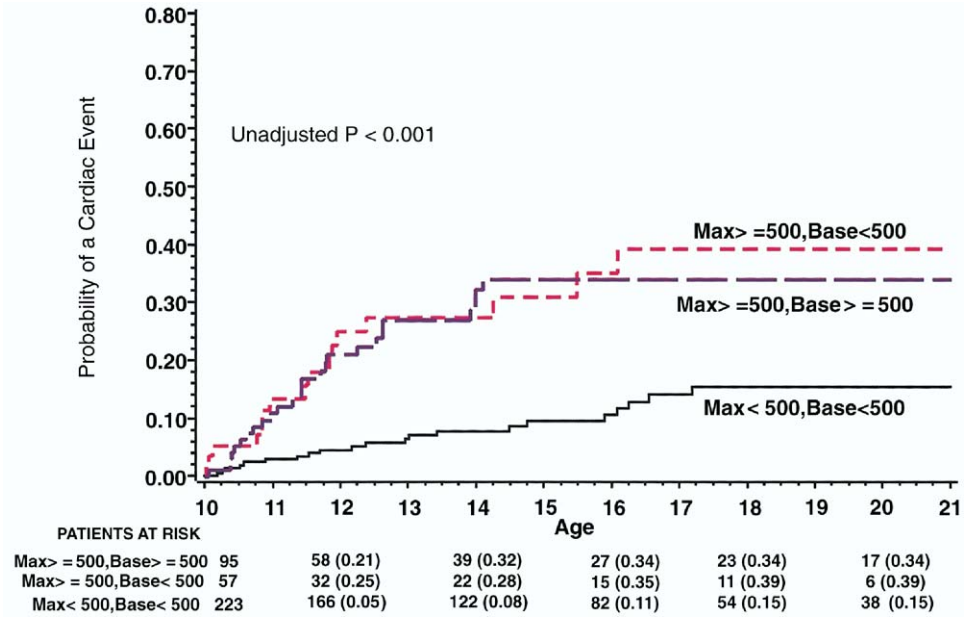

Figure 1. Kaplan-Meier estimates of the probability of a first cardiac event between ages 10 and 20 years in patients with the following combinations of corrected QT (QTc) measures: maximum QTc <500 ms and baseline QTc <500 ms; maximum QTc ≥500 ms and baseline QTc <500 ms; and maximum QTc ≥500 ms and baseline QTc ≥500 ms.

results using Bazett's formula fit the data better than those using the Fridericia formula.

Time-dependent analysis of the benefit of beta-blocker therapy demonstrated an overall 54% reduction in the risk of cardiac events during adolescence ($p = 0.01$) and an 83% risk reduction in patients with a maximum QTc duration of ≥500 ms ($p < 0.001$; p value for maximum QTc × beta-blocker therapy interaction = 0.009).

Kaplan-Meier curves describing the probability of experiencing a first cardiac event during adolescence demonstrated that patients with a maximum QTc value of ≥500 ms exhibited the highest rate of cardiac events, regardless of the baseline QTc value (Fig. 1).

Effect of the number of follow-up ECGs on the association between QTc summary measures and cardiac events. The number of ECGs recorded before age 10 and the age of the first recorded ECG were not significant predictors of cardiac events during adolescence in all multivariate models (HR = 1.01 [p = 0.73] and 1.01 [p = 0.86], respectively, in the model including a maximum QTc of ≥500 ms).

When the 4 QTc summary measures were analyzed among patients with >2 ECGs during follow-up (Table 3), a maximum QTc value of ≥500 ms recorded at any time before age 10 was consistently shown to be the most powerful predictor of cardiac events during adolescence. Notably, increasing HRs for the association between the maximum QTc interval and cardiac events were obtained with increasing number of ECGs during follow-up (Table 3).

QTc threshold and the risk of cardiac events. A baseline QTc of ≥500 ms has been shown in earlier analyses to discriminate between risk groups in LQTS patients (4–8). We examined whether this QTc threshold was also consistent for QTc intervals measured on follow-up ECGs. In this analysis, QTc was dichotomized at different values (480 to 540 ms by 10-ms intervals), and the deviances for the resulting separate multivariate Cox models were compared. When different thresholds of the maximum QTc were

Table 3. Adjusted Hazard Ratios for Cardiac Events for the 4 QTc Summary Measures Dichotomized at 500 ms Among Patients In Whom ≥3 and ≥4 ECGs Were Recorded Before Age 10*

QTc Summary Measures	HR	95% Confidence Interval	p Value
≥3 ECGs (n = 211)			
Model 1:			
Baseline QTc	1.23	0.61–2.51	0.56
Model 2:			
Mean QTc	1.47	0.72–3.00	0.29
Model 3:†			
Maximum QTc	2.81	1.28–6.16	0.01
Model 4:			
Recent QTc	1.65	0.82–3.30	0.16
≥4 ECGs (n = 138)			
Model 1:			
Baseline QTc	1.62	0.66–3.96	0.29
Model 2:			
Mean QTc	1.46	0.61–3.47	0.40
Model 3:†			
Maximum QTc	3.61	1.38–9.41	0.009
Model 4:			
Recent QTc	1.67	0.71–3.95	0.24

*Findings in each model were adjusted for the additional covariates: time-dependent beta-blocker therapy, cardiac events before age 10, the number of ECGs recorded before age 10 and the age of the first recorded ECG; similar results were obtained when the number of ECGs recorded before age 10 was categorized (2, 3 or ≥4 ECGs). Gender did not make a significant contribution to outcome in the multivariate models. †Model with the best fit as defined by the lowest deviance (−2 log likelihood).

Abbreviations as in Tables 1 and 2.

Table 4. Adjusted HR for Cardiac Events of the Maximum QTc Summary Measure, Dichotomized at Different QTc Intervals*

Threshold (n = 375)	HR	95% Confidence Interval	p Value
Maximum QTc ≥480 ms	1.83	0.98–3.45	0.06
Maximum QTc ≥490 ms	2.04	1.12–3.73	0.02
Maximum QTc ≥500 ms†	2.74	1.52–4.85	<0.001
Maximum QTc ≥510 ms†	2.76	1.56–4.87	<0.001
Maximum QTc ≥520 ms	2.35	1.35–4.11	0.002
Maximum QTc ≥530 ms	2.41	1.37–4.26	0.002
Maximum QTc ≥540 ms	2.33	1.31–4.12	0.004

*A best subsets procedure was used to compare the model fit (see text); findings in each model were adjusted for the additional covariates: time-dependent beta-blocker therapy, cardiac events before age 10, the number of ECGs recorded before age 10 and the age of the first recorded ECG; similar results were obtained when the number of ECGs recorded before age 10 was categorized (2, 3 or ≥4 ECGs). Gender did not make a significant contribution to outcome in the multivariate models. †Models with the best fit as defined by the lowest deviance (−2 log likelihood); models with maximum QTc ≥500 ms and ≥510 ms yielded virtually identical deviances.

Abbreviations as in Tables 1 and 2.

analyzed (Table 4), QTc interval durations of ≥500 ms and ≥510 ms before age 10 years were shown to be the strongest predictors of cardiac events during adolescence.

Similar analyses were performed to identify the best QTc threshold for the baseline (480 ms), mean (480 ms), and most recent (530 ms) summary measures. Consistently, a maximum QTc dichotomized at ≥500 ms maintained the best fit for the study data (−2 log likelihood = 651) compared with the best threshold of the former 3 summary measures (−2 log likelihood = 658, 655, and 654, respectively). In addition, when the maximum QTc was combined with each of the other 3 QTc summary measures with these thresholds, only the former QTc parameter was associated with a significant increase in the risk of cardiac events (data not shown).

DISCUSSION

We have shown that in patients with LQTS there is a considerable variability in QTc interval duration when serial ECGs are recorded during follow-up. This time-dependent change in QTc duration is an important determinant of the phenotypic expression of the disease. The maximum QTc duration measured at any time before age 10 was shown to be the most powerful predictor of cardiac events during adolescence, regardless of baseline, mean, or most recent QTc values.

In recent years, numerous advances have been made in the risk stratification of LQTS patients (4–8, 11–17). It has been shown that a QTc interval duration of ≥500 ms is a major risk factor for cardiac events in this population. However, earlier studies in which the association between the QTc interval duration and the risk of cardiac events was analyzed were limited mostly to a single QTc value measured in the first recorded ECG (4–8,11–17). Such an approach precludes the possibility of analyzing the effect of time-dependent change in QTc values on the risk of LQTS-related cardiac events. In addition, QTc values measured in the first recorded ECG in earlier studies were not necessarily determined before an event end point. Therefore, the interpretation of the association between QTc duration and subsequent cardiac events in previous reports may be limited by the lack of a consistent chronology between QTc measurements and events.

In the current study, we have evaluated the incremental benefit of follow-up ECG data in the risk stratification of LQTS patients. Our results show that QTc values obtained during follow-up in LQTS patients are clinically important and better define subsequent risk of cardiac events than a single baseline QTc value. In our analysis, the change in QTc values was not age-related or linear. Rather, a QTc interval duration of ≥500 ms obtained at any earlier time emerged as the best indicator of risk. Therefore, LQTS patients with a single recorded QTc value below this threshold, who are currently considered to be at a lower risk, should be continually assessed, because the phenotypic expression of this disease entity is dynamic and can change at any time during follow-up. Notably, we have shown that the improved risk stratification provided by obtaining the maximum QTc value on follow-up ECGs can be further improved by increasing the number of recorded ECGs. Thus, risk stratification, based on QTc measurements, should use repeated follow-up ECG QTc measures.

The incremental prognostic information obtained by recording follow-up QTc data draws attention to the variability present in this ECG parameter. The changes over time seen in the QTc interval highlight the fact that LQTS is a genetic disorder with variable expressivity. Increased QTc variability reflects an exaggeration of the normally heterogeneous process of ventricular repolarization. Consequently, as the cardiac action potential is prolonged, myocytes become vulnerable to re-entrant currents that can trigger early after-depolarizations and subsequent torsades de pointes tachyarrhythmias (18). This varied clinical expression, which has been shown in other studies (19,20), explains the need to examine multiple ECGs to properly assess this dynamic ECG parameter. A maximum QTc of ≥500 ms, despite lower baseline values, may signify an extremely heterogeneous repolarization state in LQTS patients which places patients with this ECG manifestation at a high risk for an arrhythmic event.

The focus of the present study was to evaluate the risk associated with QTc data. However, it should be noted that other risk factors, including a history of prior syncope, age, gender, and genotype, are associated with events in LQTS patients and may contribute to the development of fatal or nonfatal events independently of the QTc. In the current study a maximum QTc duration of ≥480 ms was associated with a meaningful, although of a lesser magnitude than with the 500-ms threshold, increase in the risk of cardiac events. Therefore, a comprehensive clinical risk assessment is especially important when borderline QTc increments are measured during follow-up.

The current data suggest that when QTc interval duration exceeds 500 ms during follow-up, even among LQTS patients in whom prior ECGs recorded lower values, primary therapy of this genetic disorder should be considered. Notably, treatment with beta-blockers was associated with a highly significant 83% reduction in the risk of cardiac events in patients with a maximum QTc of ≥500 ms. Therefore, initiation of beta-blocker therapy should be considered in all patients in whom increasing QTc durations are measured in serial ECGs, and alternative therapies, including primary defibrillator implantation, may be warranted in patients with increasing QTc values and recurrent nonfatal events despite beta-blocker therapy.

Study limitations. In the current study we analyzed the risk of cardiac events during adolescence, because this time period has been shown to be associated with a relatively high rate of LQTS-related events. The generalizability of our findings to other age groups should be evaluated in future studies.

Patients were included in the study if ≥2 ECGs were recorded before age 10 years. Therefore, the study cohort may represent a higher-risk LQTS subset. This potential bias was perhaps partially ameliorated by adjusting for earlier cardiac events, the number of recorded ECGs before age 10 years, and the age of the first recorded ECG in the multivariate Cox regression models.

Owing to the relatively small number of study patients who were genotyped, the relationship between specific LQTS genotypes and the prognostic implication of long-term QTc change was not assessed. Genotype has been shown to affect the clinical course of LQTS (1–5,13–17), and future efforts to relate genetic data to long-term ECG follow-up may improve risk assessment of LQTS patients.

Forty-one percent of the study patients had a maximum QTc of >500 ms, whereas only 25% of the patients had a baseline QTc of >500 ms. We have shown that these incremental ECG data during childhood have important prognostic implications during adolescence, which are even more important than the information obtained from the last recorded ECG before adolescence. However, we did not evaluate the effect of time-dependent changes in QTc duration during adolescence on the risk of subsequent cardiac events. It is possible that QTc decrements reported in boys during this time-period (13) are also associated with a reduction in risk. The current data suggest that QTc should be evaluated as a time-dependent risk factor in future studies of LQTS patients.

Conclusions. We have shown that in LQTS patients, a QTc duration of ≥500 ms at any time during follow-up is associated with an increased risk of subsequent cardiac events, regardless of the baseline QTc value. Our findings suggest that QTc data from follow-up ECGs have important incremental prognostic value and should be incorporated into the risk stratification of LQTS patients in view of the dynamic phenotypic expression of this genetic disorder.

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